Ethyl 3,3-diamino-2-(2-*p*-tolylpyrimidin-4-yl)acrylate, a new representative of hetarylketene aminals

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A new representative of hetarylketene aminals, ethyl 3,3-diamino-2-(2-*p*-tolylpyrimidin-4-yl)acrylate, was synthesized by the reaction of *p*-toluamidine with the condensation product of dimethylformamide dimethyl acetal and the difluoroboron chelate of acetyl(ethoxycarbonyl)ketene (*N*-benzoyl)aminal. This synthesis is an example of pyrimidine ring assembly using the methodology based on transformations of chelate complexes.

Key words: α,α-dioxoketene aminals; difluoroboron chelates; hetarylketene aminals; ethyl 3,3-diaminoacrylate; *p*-toluamidine; pyrimidine; chelate synthesis.

α,α-Dioxoketene aminals, easily obtained from β-dicarbonyl compounds and cyanamides,[1—4] form chelate boron complexes,[1,5—8] which differ in reactivity from the initial ligands. This feature could form the foundation of an approach to non-standard variants of delicate organic syntheses involving the transformations of chelates, which are not typical for free ketene aminals.

Earlier we proposed an original scheme for the preparation of 4-pyridone derivatives from diacetylketene aminals *via* their difluoro- and diphenylboron chelates.[5] The key step of the synthesis is the condensation of the latter with amide acetals, in which the Me group linked directly to the chelate cycle is involved.

We have described the formation of tetrahydroquinazoline and tetrahydroindazole ring systems from ketene aminal obtained from 1,3-cyclohexanedione and benzoylcyanamide, *via* its diphenylboron chelate. The reaction of the latter with amide acetals proceeds with participation of the methylene group of the cyclohexane ring. Treatment of the condensation products with hydrazine results in the formation of derivatives of tetrahydro-2*H*-indazol-6-one,[6] whereas heating with *p*-toluamidine gives 8-(*N*-benzoyldiaminomethylene)-2-*p*-tolyl-5,6,7,8-tetrahydroquinazolin-7-one.[8]

A similar approach was used in this work for transformation of acetyl(ethoxycarbonyl)ketene (*N*-benzoyl)aminal (**1**) (Scheme 1) to ethyl 3,3-diamino-2-(2-*p*-tolylpyrimidin-4-yl)acrylate (**5**), which can be considered as a new reagent belonging to the class of hetarylketene aminals.

A convenient method of aminal **1** synthesis is based on the reaction of acetoacetate with benzoylcyanamide[2] in the presence of catalytic amounts of $Ni(acac)_2$. Treatment of ketene aminal **1** with $BuOBF_2$ results in the formation of chelate complex **2**. After refluxing with dimethylformamide dimethylacetal (DMF DMA) in THF, chelate complex **2** gives the condensation product **3**, which also has a chelate structure (see Scheme 1). The reaction of **3** with *p*-toluamidine under reflux in THF gives rise to the corresponding pyrimidine (**4**). Debenzoylation of compound **4** to the product **5** can be easily performed with MeONa in MeOH.

Chelate **2** is a white crystalline substance, easily soluble in $CHCl_3$ and C_6H_6 at ~20 °C and in THF when heated. In its mass spectrum the molecular ion peak is observed (*m/z* 324), and in the ^{11}B NMR spectrum there is a high field signal (δ −0.7) corresponding to the tetra-coordinated B atom. The ^{13}C NMR spectrum of **2** suggests the participation of the acetyl group of ligand **1** in chelation. The MeCO signal in the spectrum of complex **2** (δ 188.15) is significantly shifted upfield in comparison to the corresponding signal of the free ketene aminal **1** (δ 199),[2] while the chemical shifts of COOEt in the spectra of compounds **1** and **2** are close (*cf.* data[8] concerning the change in the chemical shift of the carbonyl C atom of α-oxoketene aminals on chelation).

Chelate complex **3** (a product of the reaction of **2** with DMF DMA) is a yellow crystal substance, easily soluble in $CHCl_3$, C_6H_6, DMF and sparingly soluble in acetone, THF, and EtOH. Its structure was confirmed by NMR (^1H, ^{13}C), and IR spectroscopy and mass spectrometry. The ^1H NMR spectrum of compound **3** in $CDCl_3$ is characterized by the presence of methyl group signals (δ 2.95 and 3.20) and doublets of CH groups (δ 6.05 and 8.02).

The transformation of chelate **3** to ketene aminal **4** may be the result of replacement of the Me_2N group by *p*-toluamidine, template formation of the pyrimidine ring, and destruction of the chelate complex (deboration)

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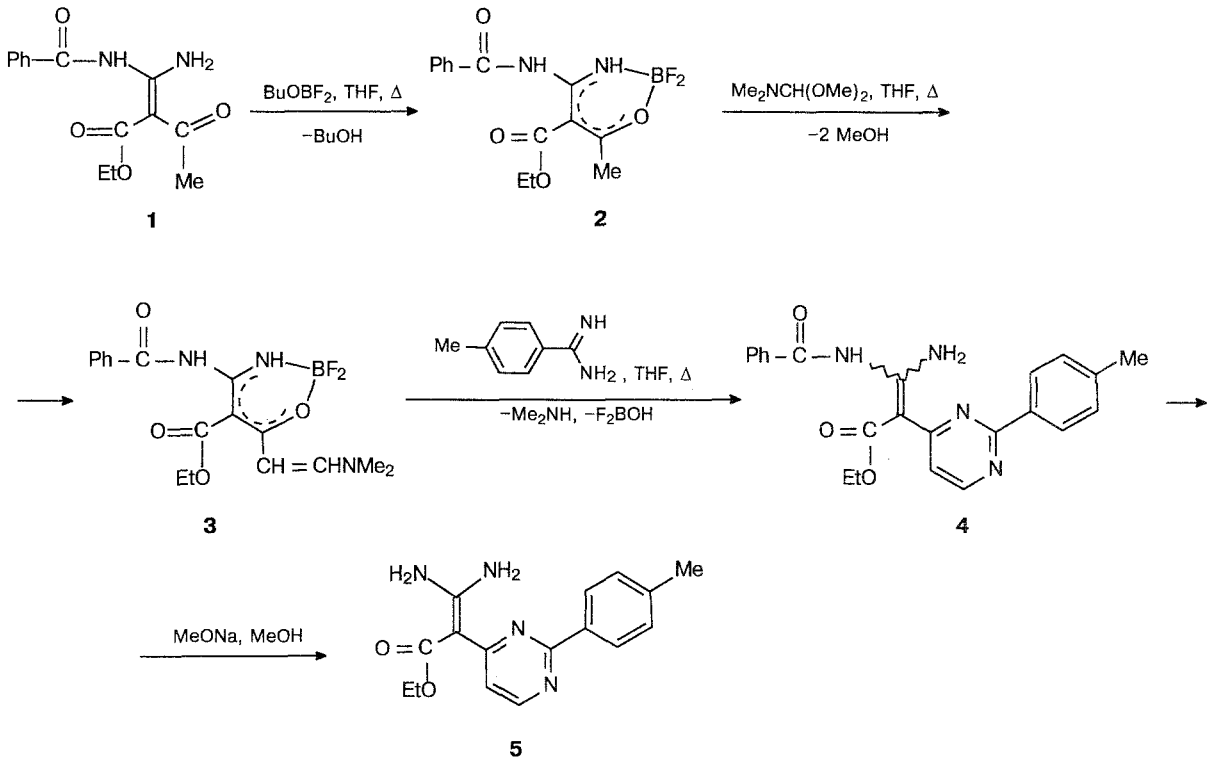
Scheme 1



by the water formed in the cyclization. The yield of compound **4** reaches 55 %.

The structure of pyrimidinylacrylates **4** and **5** was confirmed by NMR (^{1}H, ^{13}C), IR spectroscopy, and mass spectrometry. In the ^{1}H NMR spectrum of compound **4** only one series of signals is observed. This may be explained either by the presence of only the *E*- or *Z*-form in solution, or by a low barrier to rotation about the C=C bond.

Ketene aminals **4** and **5** are white crystalline substances soluble in $CHCl_3$ and C_6H_6; compound **5** is much more soluble than **4** in EtOH, MeCN, and THF.

The proposed synthesis of pyrimidine derivatives **4** and **5** is a new example of the construction of heterocycles from α,α-dioxoketene aminals based on the "methodology of chelate organic synthesis" (*cf.* Ref. 8).

Compound **5** unsubstituted at the N atoms of the diaminomethylene fragment could be used (like ketene aminals of type **1**) as a reagent for heterocycle synthesis (*cf.* Ref. 9).

Experimental

^{1}H NMR spectra were recorded on a Bruker WM-250 instrument, and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer. IR spectra were obtained with a UR-20 instrument, and mass spectra were obtained on a Varian MAT-311A (70 eV) mass spectrometer.

Ketene aminal **1** was synthesized according to the known procedure,[2] and butoxydifluorborane was obtained as described earlier.[10]

{Ethyl [2-(*N*-benzoyldiaminomethylene)acetoacetato-*O,N*]}difluoroboron (2). A solution of ketene aminal **1** (0.34 g, 1.23 mmol) and $BuOBF_2$ (0.53 mL) in THF (10 mL) was refluxed for 5 h and then left over night. The precipitated crystals were filtered off and recrystallized from MeCN to give chelate **2** (0.32 g, 80 %, m.p. 179—181 °C). Found (%): C, 52.15; H, 4.51; N, 8.41. $C_{14}H_{15}BF_2N_2O_4$. Calculated (%): C, 51.88; H, 4.67; N, 8.65. MS, *m/z*: 324 $[M]^{+\cdot}$. IR ($CHCl_3$), ν/cm^{-1}: 3264 (NH); 3180—2830 (NH, CH); 1694, 1686, 1628, 1610, 1562, 1556. ^{11}B NMR ($CDCl_3$), δ: −0.7. ^{1}H NMR ($CDCl_3$), δ: 1.40 (m, 3 H, Me); 2.60 (s, 3 H, MeCO); 4.40 (q, 2 H, CH_2); 7.52 (m, 2 H, Ph); 7.60—7.98 (m, 3 H, Ph); 10.73 (br.s, 1 H, NH); 13.28 (s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 14.14 (q, Me, ^1J = 128 Hz); 27.42 (q, MeCOB, ^1J = 131 Hz); 62.31 (t, CH_2, ^1J = 148 Hz); 93.62 (s, CCOO); 127.79, 129.32, 131.52, 134.21 (Ph); 159.51 (s, NCN); 168.84 (s) and 169.02 (t) (NCO, COO, ^3J = 4 Hz); 188.15 (q, COB, ^2J = 6 Hz).

{Ethyl [2-(*N*-benzoyldiaminomethylene)-5-dimethylamino-3-oxo-4-pentenoato-*O,N*]}difluoroboron (3). A solution of chelate **2** (0.32 g, 0.99 mmol) and DMF DMA (0.26 mL, 2.20 mmol) in THF (4 mL) was refluxed for 6 h then left over night. The precipitated crystals were filtered off. An additional amount of product was isolated from the filtrate by column chromotography (SiO_2, $CHCl_3$). Yield of chelate **3** was 0.29 g (78 %), m.p. 214—215 °C (benzene). MS, *m/z*: 379 $[M]^{+\cdot}$. IR ($CHCl_3$), ν/cm^{-1}: 3284 (NH); 3190—2830 (NH, CH); 1686, 1670 (CO); 1582, 1560, 1504. ^{1}H NMR ($CDCl_3$), δ: 1.40 (t, 3 H, Me); 2.95 (s, 3 H, MeN); 3.20 (s, 3 H, MeN); 4.35 (q, 2 H, CH_2); 6.10 (d, 1 H, CH, J = 11 Hz); 7.50—7.70 (m, 3 H, Ph); 7.99 (m, 2 H, Ph); 8.02 (d, 1 H, CH); 10.30 (br.s, 1 H, NH); 13.60 (s, 1 H,NH).

Ethyl 3,3-(*N*-benzoyl)diamino-2-(2-*p*-tolylpyrimidin-4-yl)acrylate (4). A mixture of chelate **3** (0.29 g, 0.75 mmol) and *p*-toluamidine (0.10 g, 0.75 mmol) in THF (10 mL) was

refluxed for 12h (three more portions of *p*-toluamidine (0.09 g, 0.69 mmol) were added). The mixture was cooled to ~20 °C, filtered, and the filtrate was evaporated. The residue was dissolved in benzene and chromatographed on SiO_2 (eluent — C_6H_6). The solvent was distilled off, the residue was crystallized by trituration with pentane, and the crystals were filtered off and washed with pentane. The yield of ester **4** was 0.17 g (55 %), m.p. 144—146 °C (MeCN). Found (%): C, 68.65; H, 5.99; N, 14.06. $C_{23}H_{22}N_4O_3$. Calculated (%): C, 68.64; H, 5.51; N, 13.92. MS, *m/z*: 402 $[M]^{+\cdot}$. IR (CH_2Cl_2), ν/cm^{-1}: 3360 (NH); 3200—2800 (NH, CH); 1680 (CO); 1640—1612, 1580, 1565. ^1H NMR (DMSO-d_6), δ: 1.26 (t, 3 H, Me); 2.37 (s, 3 H, $\underline{Me}C_6H_4$); 4.25 (q, 2 H, CH_2); 7.26 (d, 2 H, C_6H_4); 7.45 (m, 2 H, Ph); 7.55 (d, 1 H, CH, J = 7 Hz); 7.65 (m, 1 H, Ph); 7.84 (m, 2 H, Ph); 8.10 (d, 2 H, C_6H_4); 8.62 (d, 1 H, CH); 9.50 (br.s, 1 H, NH); 13.92 (s, 1 H, NH).

Ethyl 3,3-diamino-2-(2-*p*-tolylpyrymidin-4-yl)acrylate (5). A mixture of ester **4** (0.17 g, 0.42 mmol) and MeONa (obtained from Na (0.01 g, 0.43 mmol) and MeOH (10 mL)) was stirred at 60 °C for 20 min, then cooled to ~20 °C and acidified with AcOH. The solvent was distilled off *in vacuo*, and a heptane—ether mixture (1:10, 5 mL) was added to the residue and then filtered. The substance on the filter was washed with water and dried to give 0.09 g (71 %) of ester **5**, m.p. 147—148 °C (benzene—heptane, 1:1). Found (%): C, 64.30; H, 6.18; N, 18.51. $C_{16}H_{18}N_4O_2$. Calculated (%): C, 64.40; H, 6.08; N, 18.78. MS, *m/z*: 298 $[M]^{+\cdot}$. IR ($CHCl_3$), ν/cm^{-1}: 3488, 3400—2900 br (NH, CH); 1640 (CO); 1610, 1585, 1560. ^1H NMR ($CDCl_3$), δ: 1.38 (t, 3 H, Me); 2.43 (s, 3 H, $\underline{Me}C_6H_4$); 4.30 (q, 2 H, CH_2); 7.05 (br.s, 2 H, 2 NH); 7.30 (d, 2 H, C_6H_4); 7.55 (d, 1 H, CH, J = 7 Hz); 7.80 (br.s, 2 H, 2 NH); 8.12 (d, 2 H, C_6H_4); 8.45 (d, 1 H, CH). ^{13}C NMR ($CDCl_3$), δ: 14.57 (q, Me, ^1J = 127 Hz); 21.37 (qt, $\underline{Me}C_6H_4$, ^1J = 126 Hz, ^2J = 4 Hz); 59.50 (tq, CH_2, ^1J = 147 Hz, ^2J = 5 Hz); 80.21 (s, $\underline{C}CO$); 118.34 (dd, C-5', ^1J = 170 Hz, ^2J = 8 Hz); 127.69, 129.48, 135.93, 140.47 (C_6H_4); 154.33 (br.d, C-6', ^1J = 177 Hz); 162.00 (dt, C-2', ^3J = 10 Hz, ^3J = 4 Hz); 163.23 (s, NCN); 165.95 (d, C-4', J = 6 Hz); 170.55 (s, CO).

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